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DIMERIC AZACYCLIC COMPOUNDS AND THEIR USE**TECHNICAL FIELD**

5 This invention relates to novel azacyclic derivatives and their use as pharmaceuticals. Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine
10 diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

BACKGROUND ART

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The endogenous cholinergic neurotransmitter, acetylcholine, exerts its biological effect via two types of cholinergic receptors, the muscarinic Acetyl Choline Receptors (mAChR) and the nicotinic Acetyl Choline Receptors (nAChR).

It is well established that muscarinic acetylcholine receptors are of
20 importance in relation to memory and cognition, and much research aimed at the development of agents for the treatment of memory related disorders have focused on the synthesis of muscarinic acetylcholine receptor modulators.

Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency.

25 *Brown et al.* [*Brown et al.*: Quinuclidine Inhibitors of 2,3-Oxidosqualene Cyclase-Lanosterol Synthase: Optimization from Lipid Profiles; *J. Med. Chem.* 1999 **42** 1306-1311] describe the synthesis of 3-substituted quinuclidine derivatives useful as inhibitors of the cholesterol biosynthesis. An effect on the nicotinic and/or the monoamine receptors is not reported.

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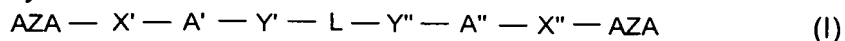
SUMMARY OF THE INVENTION

The present invention is devoted to the provision of new azacyclic derivatives that are modulators of the nicotinic and/or of the monoamine receptors,
35 and which modulators are useful for the treatment of diseases or disorders related to the cholinergic receptors, and in particular the nicotinic acetylcholine receptor, the monoamine receptors, in particular the serotonin receptor (5-HT₁), the dopamine receptor (DAR) and the norepinephrine receptor (NER), and of the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and norepinephrine (NE).

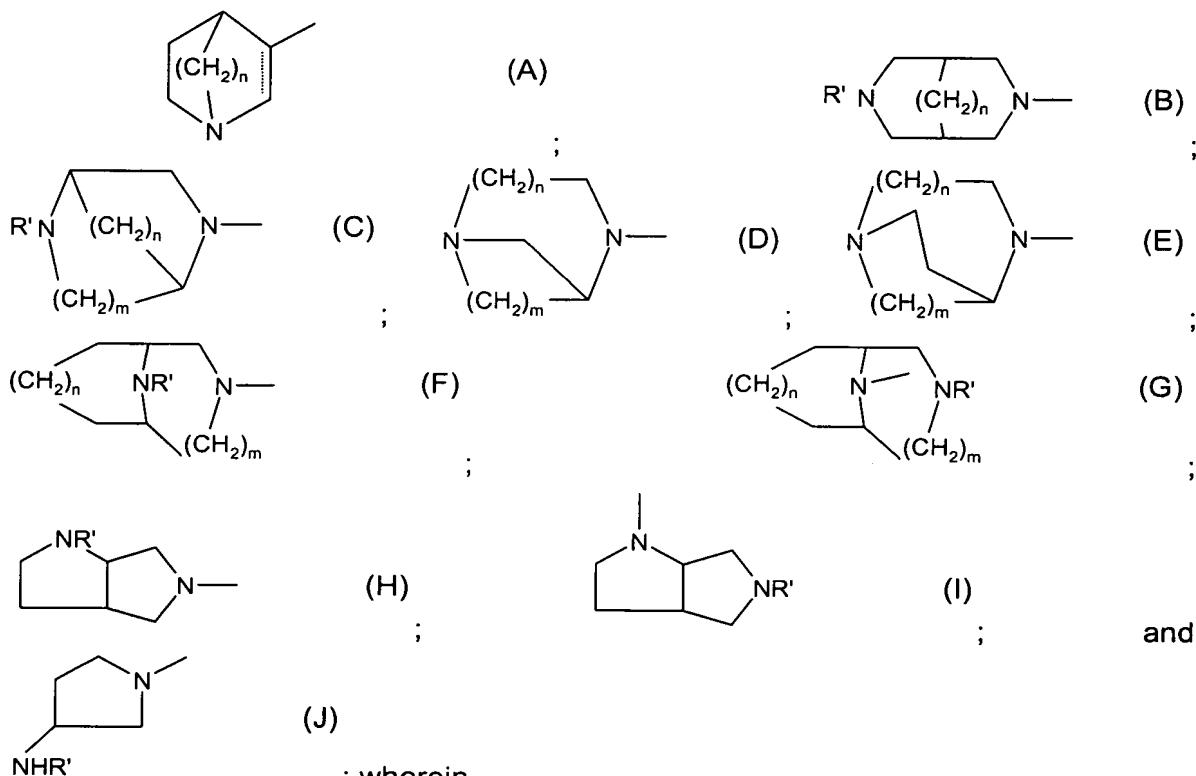
Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

The compounds of the invention may also be useful as diagnostic tools or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging), and they may be used in labelled or unlabelled form.

Accordingly, in its first aspect the invention provides azacyclic derivatives represented by Formula I



an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein, AZA represents an azacyclic group selected from



----- represents an optional double bond;

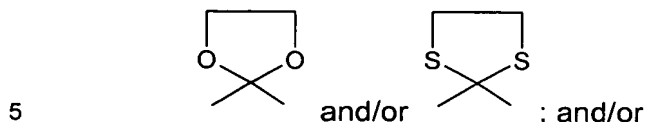
n is 0, 1, 2 or 3;

m is 1 or 2; and

R' represents hydrogen or alkyl;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

A' and A'', independently of one another, represent an aromatic monocyclic
10 and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic,
15 carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido,
20 sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of
25 alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with
30 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from
35 -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



and/or ; and/or

a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

- 5 L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, 10 sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl. 15

In another aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the azacyclic derivative of the invention.

- In a third aspect the invention relates to the use of the azacyclic derivative of 20 the invention, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the action of a nicotinic acetylcholine receptor modulator.

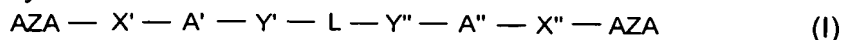
- 25 In a further aspect the invention provides a method of the treatment or alleviation of a disease or disorder of a living animal body, including a human, which disease or disorder is responsive to the action of a nicotinic acetylcholine receptor modulator, which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of the 30 azacyclic derivative of the invention.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

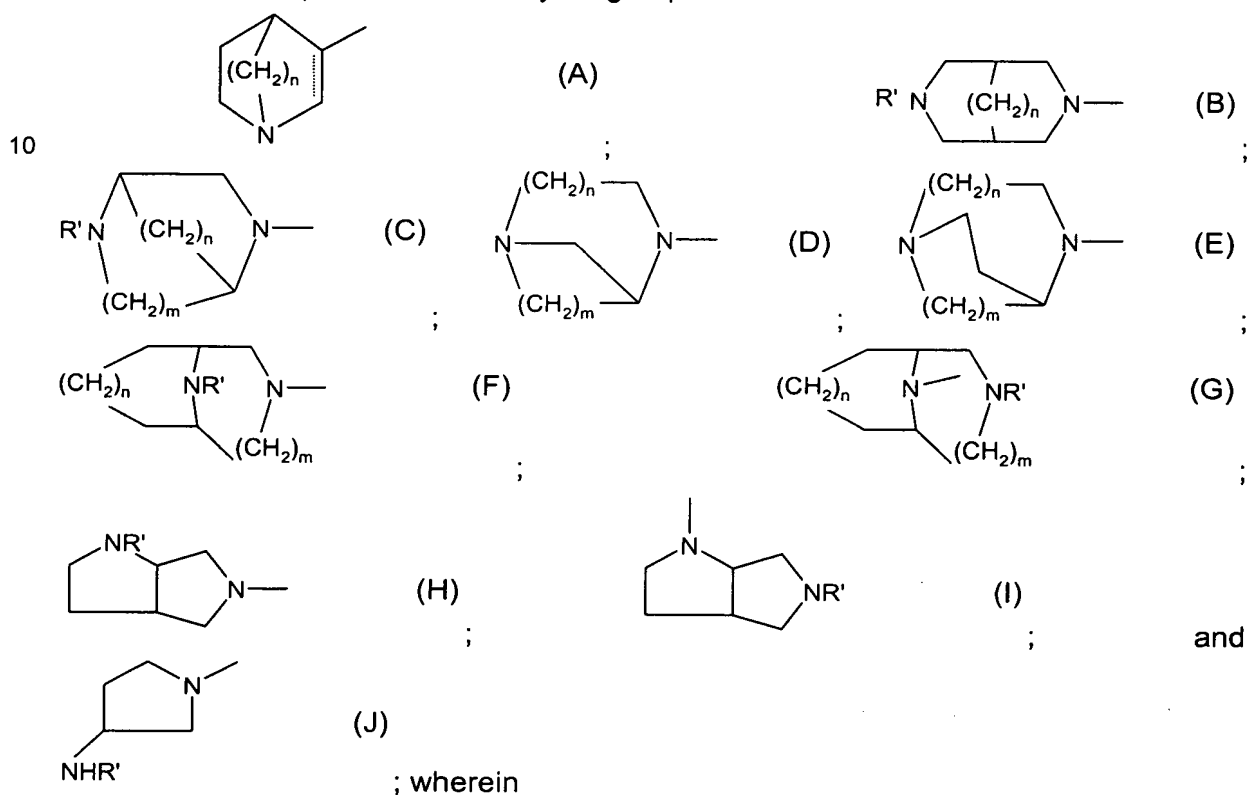
Azacyclic Derivatives

In its first aspect, the present invention provides novel azacyclic derivatives
5 represented by Formula I



an enantiomer thereof, or a mixture of its enantiomers, or a
pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

AZA represents an azacyclic group selected from



15 ----- represents an optional double bond;

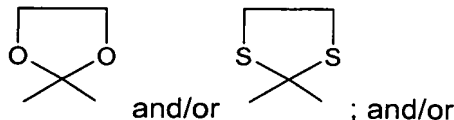
n is 0, 1, 2 or 3;

m is 1 or 2; and

R' represents hydrogen or alkyl;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

20 X' and X'', independently of one another, represent a linker selected from
-O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-,
-NH-, -N(alkyl)-, -(CO)-, -(CS)-,



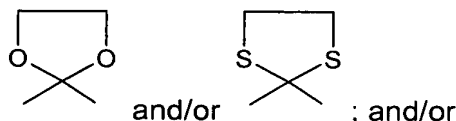
a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from -O- , $\text{-O-CH}_2\text{-}$, $\text{-O-CH}_2\text{-CH}_2\text{-}$, -S- , -SO- , $\text{-SO}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-S-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-(C=CH}_2\text{)-}$, -NH- , -N(alkyl)- , -(CO)- , -(CS)- ,

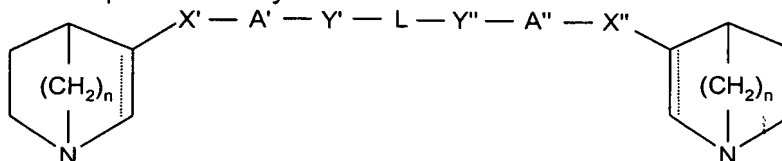


a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with

substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a preferred embodiment the azabicyclic derivative of the invention is an azacyclic derivative represented by Formula II



(II)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

----- represents an optional double bond;

n is 1, 2 or 3;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'', independently of one another, represent a linker selected from

-O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-,

-(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



and/or ; and/or

a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

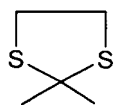
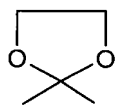
A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with

substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

5 Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,

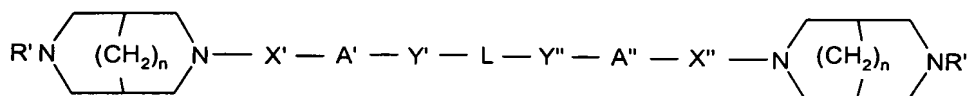


and/or ; and/or

a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

25 L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a third preferred embodiment the azabicyclic derivative of the invention is represented by Formula III



(III)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

R' represents hydrogen or alkyl;

5 n is 1, 2 or 3;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



10 and/or ; and/or

a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

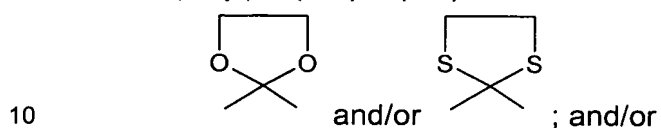
A' and A'', independently of one another, represent an aromatic monocyclic
15 and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic,
20 carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido,
25 sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of
30 alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or

polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

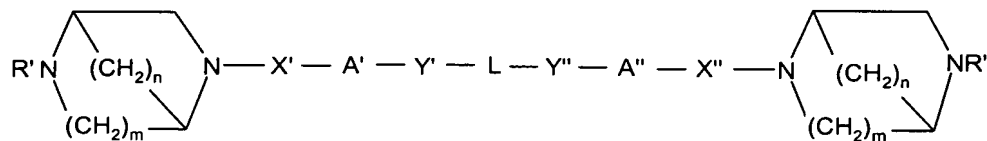
Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

25 In a fourth preferred embodiment, the azabicyclic derivative of the invention is represented by Formula IV,



(IV)

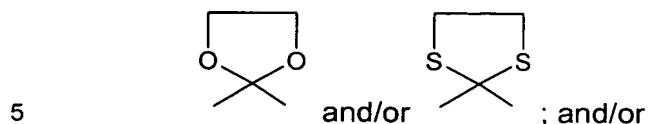
an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

30 n is 1 or 2;

m is 1 or 2;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

A' and A'', independently of one another, represent an aromatic monocyclic
10 and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic,
15 carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido,
20 sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of
25 alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with
30 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from
35 -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,

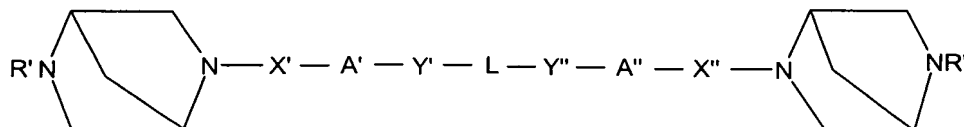


and/or ; and/or

a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

- 5 L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, 10 sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl. 15

In a fifth preferred embodiment the azabicyclic derivative of the invention is represented by Formula IVa,



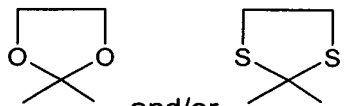
(IVa)

an enantiomer thereof, or a mixture of its enantiomers, or a 20 pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

R' represents hydrogen or alkyl;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'' , independently of one another, represent a linker selected from 25 -O- , $\text{-O-CH}_2\text{-}$, $\text{-O-CH}_2\text{-CH}_2\text{-}$, -S- , -SO- , $\text{-SO}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-S-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-(C=CH}_2\text{)-}$, -NH- , -N(alkyl)- , -(CO)- , -(CS)- ,



and/or ; and/or

a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, 5 cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, 10 hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

L represents a single (covalent) bond (i.e. L is absent); or a group A''' which 15 represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or 20 polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, 25 sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



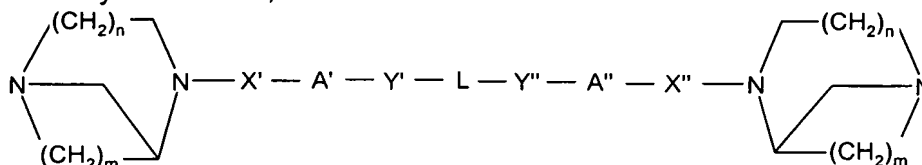
and/or ; and/or

30 a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with 35 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido,

sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a sixth preferred embodiment, the azabicyclic derivative of the invention is represented by Formula V,



(V)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

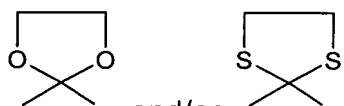
n is 1, 2 or 3;

m is 1 or 2;

R' represents hydrogen or alkyl;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



and/or ; and/or

a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl,

hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

- 5 L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 ,
 10 carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-
 15 alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,

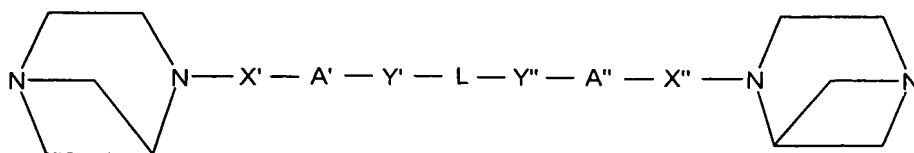


- 20 and/or ; and/or

a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR''; and R''' represents hydrogen, alkyl or cyano; and

- L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or
 25 heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl.
 30

- 35 In a seventh preferred embodiment the azabicyclic derivative of the invention is represented by Formula Va,



(Va)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

X' and X'' are absent (i.e. represent single (covalent) bonds); or

- 5 X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



and/or ; and/or

- a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and
- 10

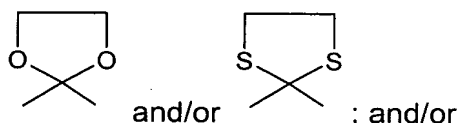
- A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with
- 15
- substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; and
- 20

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

- 25 L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with
- 30

substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

- 5 Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



- a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and
- 10

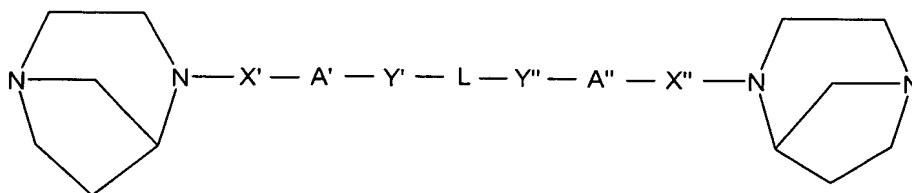
L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents

15

selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl.

20

In an eighth preferred embodiment the azabicyclic derivative of the invention is represented by Formula Vb,



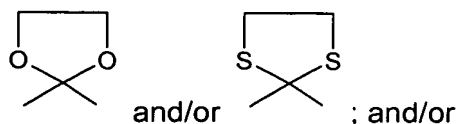
25

(Vb)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

X' and X'' are absent (i.e. represent single (covalent) bonds); or

- X' and X'', independently of one another, represent a linker selected from
- 30 -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



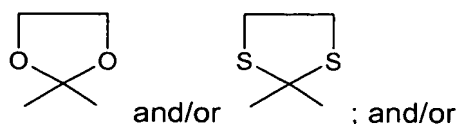
a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

- 5 A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

- L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

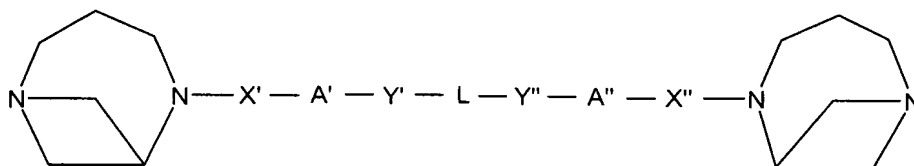
- 30 Y' and Y'', independently of one another, represent a linker selected from -O- , $\text{-O-CH}_2\text{-}$, $\text{-O-CH}_2\text{-CH}_2\text{-}$, -S- , -SO- , $\text{-SO}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-S-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-(C=CH}_2\text{)-}$, -NH- , -N(alkyl)- , -(CO)- , -(CS)- ,



a group of the formula $-\text{NR}''-(\text{CO})-$, $-\text{NR}''-(\text{CO})-\text{O}-$, $-\text{NR}''-(\text{SO}_2)-$ and $-\text{NR}''-(\text{C}=\text{Z}')-\text{NR}''-$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a ninth preferred embodiment, the azabicyclic derivative of the invention is represented by Formula Vc,

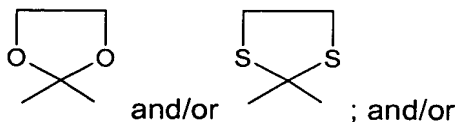


(Vc)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'' , independently of one another, represent a linker selected from $-\text{O}-$, $-\text{O}-\text{CH}_2-$, $-\text{O}-\text{CH}_2-\text{CH}_2-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{CH}_2-$, $-\text{S}-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-$, $-(\text{C}=\text{CH}_2)-$, $-\text{NH}-$, $-\text{N}(\text{alkyl})-$, $-(\text{CO})-$, $-(\text{CS})-$,



a group of the formula $-\text{NR}''-(\text{CO})-$, $-\text{NR}''-(\text{CO})-\text{O}-$, $-\text{NR}''-(\text{SO}_2)-$ and $-\text{NR}''-(\text{C}=\text{Z}')-\text{NR}''-$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

A' and A'' , independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy,

cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with

5 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

10 L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 ,

15 carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-

20 alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



25 and/or ; and/or

a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

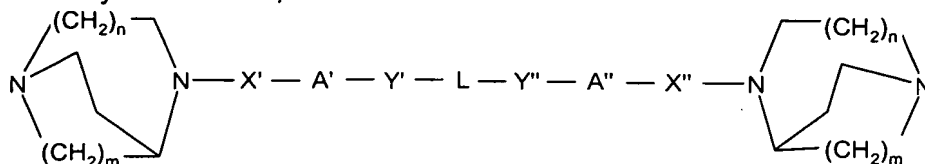
L represents a group A''' which represents a monocyclic or polycyclic,

30 carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or

35 heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy,

hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a tenth preferred embodiment the azabicyclic derivative of the invention is represented by Formula VI,



(VI)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

n is 1, 2 or 3;

m is 1 or 2;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'' , independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



and/or ; and/or

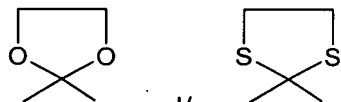
a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

A' and A'' , independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,

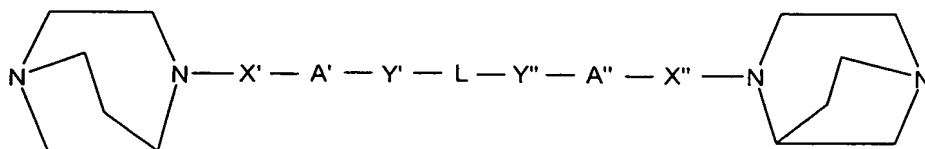


and/or ; and/or

a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In an eleventh preferred embodiment the azabicyclic derivative of the invention is represented by Formula VIa,

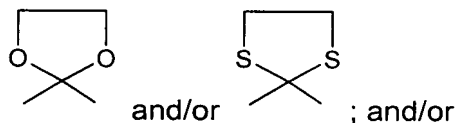


(VIa)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

X' and X'' are absent (i.e. represent single (covalent) bonds); or

- 5 X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



- a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

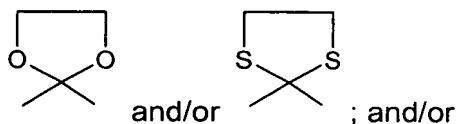
- A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with
- 15 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

- 25 L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic,
- 30

carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

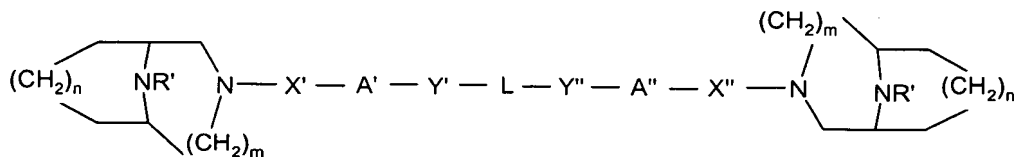
Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a twelfth preferred embodiment the azabicyclic derivative of the invention is represented by Formula VII,



(VII)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

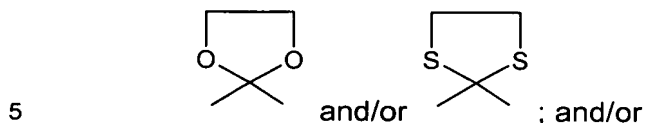
R' represents hydrogen or alkyl;

n is 1, 2 or 3;

m is 1 or 2;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

A' and A'', independently of one another, represent an aromatic monocyclic
10 and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic,
15 carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido,
20 sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of
25 alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with
30 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from
35 -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,

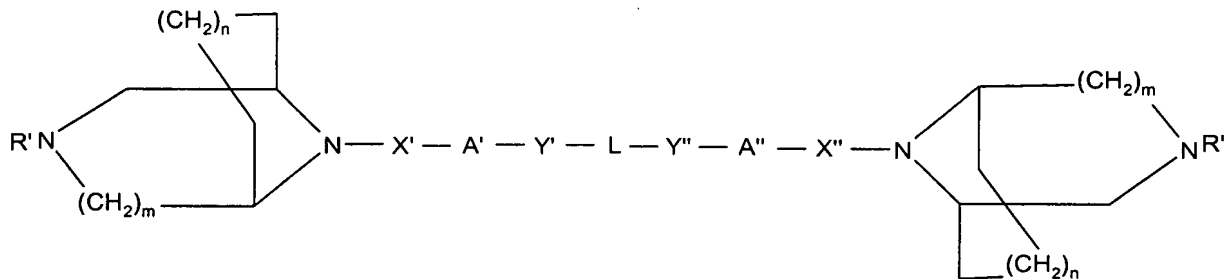


and/or ; and/or

a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

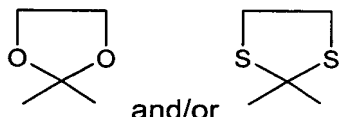
- 5 L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a thirteenth preferred embodiment the azabicyclic derivative of the invention is represented by Formula VIII,



(VIII)

- 20 an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,
 R' represents hydrogen or alkyl;
 n is 1, 2 or 3;
 m is 1 or 2;
 25 X' and X'' are absent (i.e. represent single (covalent) bonds); or
 X' and X'' , independently of one another, represent a linker selected from
 -O- , $\text{-O-CH}_2\text{-}$, $\text{-O-CH}_2\text{-CH}_2\text{-}$, -S- , -SO- , $\text{-SO}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-S-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-(C=CH}_2\text{)-}$,
 -NH- , -N(alkyl)- , -(CO)- , -(CS)- ,



and/or ; and/or

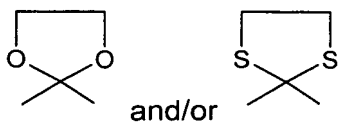
a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

- 5 A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

- L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

- 30 Y' and Y'', independently of one another, represent a linker selected from -O- , $\text{-O-CH}_2\text{-}$, $\text{-O-CH}_2\text{-CH}_2\text{-}$, -S- , -SO- , $\text{-SO}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-S-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-(C=CH}_2\text{)-}$, -NH- , -N(alkyl)- , -(CO)- , -(CS)- ,

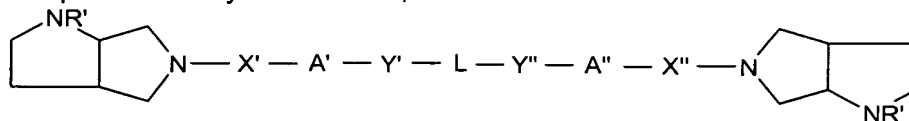


and/or ; and/or

a group of the formula $-\text{NR}''-(\text{CO})-$, $-\text{NR}''-(\text{CO})-\text{O}-$, $-\text{NR}''-(\text{SO}_2)-$ and $-\text{NR}''-(\text{C}=\text{Z}')-\text{NR}'''-$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a fourteenth preferred embodiment the azabicyclic derivative of the invention is represented by Formula IX,



(IX)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

R' represents hydrogen or alkyl;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'' , independently of one another, represent a linker selected from $-\text{O}-$, $-\text{O}-\text{CH}_2-$, $-\text{O}-\text{CH}_2-\text{CH}_2-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{CH}_2-$, $-\text{S}-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-$, $-(\text{C}=\text{CH}_2)-$, $-\text{NH}-$, $-\text{N}(\text{alkyl})-$, $-(\text{CO})-$, $-(\text{CS})-$,



and/or ; and/or

a group of the formula $-\text{NR}''-(\text{CO})-$, $-\text{NR}''-(\text{CO})-\text{O}-$, $-\text{NR}''-(\text{SO}_2)-$ and $-\text{NR}''-(\text{C}=\text{Z}')-\text{NR}'''-$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano; and

A' and A'' , independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy,

cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with

5 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

10 L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 ,

15 carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-

20 alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



25 and/or ; and/or

a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

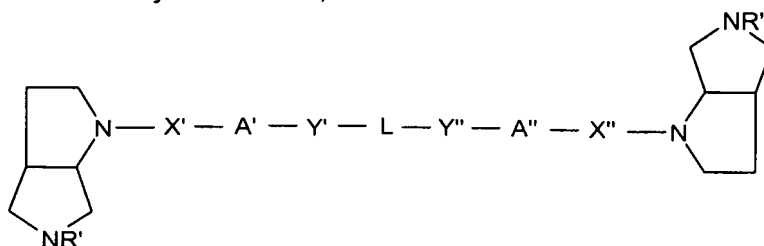
L represents a group A''' which represents a monocyclic or polycyclic,

30 carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN , NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or

35 heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy,

hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a fifteenth preferred embodiment the azabicyclic derivative of the invention is represented by Formula X,



(X)

an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

R' represents hydrogen or alkyl;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



and/or ; and/or

a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

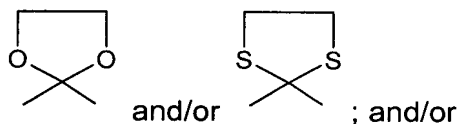
A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally

substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; or

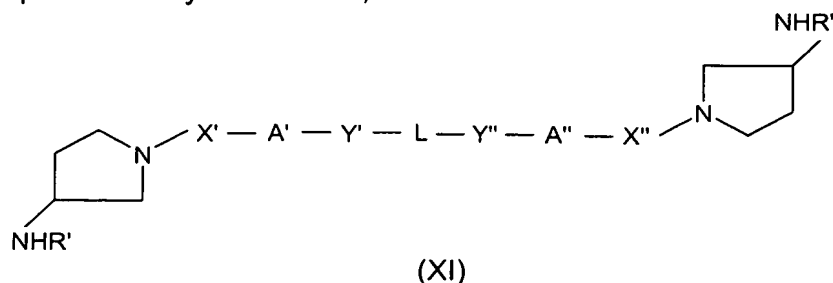
Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR''; and R''' represents hydrogen, alkyl or cyano; and

L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a sixteenth preferred embodiment the azabicyclic derivative of the invention is represented by Formula XI,

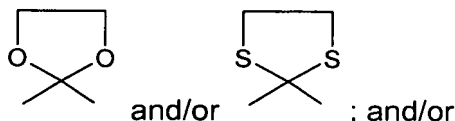


an enantiomer thereof, or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof, wherein,

R' represents hydrogen or alkyl;

X' and X'' are absent (i.e. represent single (covalent) bonds); or

- 5 X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



- 10 a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

- A' and A'', independently of one another, represent an aromatic monocyclic and/or polycyclic, carbocyclic and/or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, 15 cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with 20 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl; and

Y' and Y'' may be absent (i.e. represent single (covalent) bonds); and

- 25 L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, 30 carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, 35 sulfamoyl and phenyl; or

Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



and/or ; and/or

- 5 a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano; and

L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with
 10 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or
 15 heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

In a seventeenth preferred embodiment the azabicyclic derivative of the
 20 invention is a compound of Formula I or II, wherein ----- represents a single (covalent) bond.

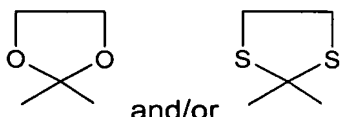
In an eighteenth preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I, II, III, VI, V, VI, VII or VIII, wherein n is 1, 2 or 3. In a more preferred embodiment the azabicyclic derivative of the invention is a
 25 compound of Formula I, II, III, VI, V, VI, VII or VIII, wherein n is 1 or 2. In a most preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I, II, III, VI, V, VI, VII or VIII, wherein n is 2.

In a nineteenth preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I, IV, V, VI, VII or VIII, wherein m is 1 or 2. In a
 30 more preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I, IV, V, VI, VII or VIII, wherein m is 2.

In a twentieth preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I-XI, wherein

X' and X'' are absent (i.e. represent single (covalent) bonds); or

- 35 X' and X'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,

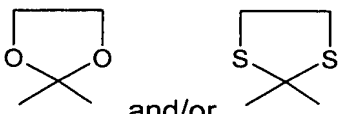


and/or ; and/or

a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano.

5 In a more preferred embodiment the X' and X'' are absent (i.e. represent single (covalent) bonds).

In another preferred embodiment X' and X'' , independently of one another, represent a linker selected from -O- , $\text{-O-CH}_2\text{-}$, $\text{-O-CH}_2\text{-CH}_2\text{-}$, -S- , -SO- , $\text{-SO}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-S-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-}$, $\text{-(C=CH}_2\text{)-}$, -NH- , -N(alkyl)- , -(CO)- , -(CS)- ,



and/or ; and/or

10

a group of the formula $\text{-NR}''\text{-(CO)-}$, $\text{-NR}''\text{-(CO)-O-}$, $\text{-NR}''\text{-(SO}_2\text{)-}$ and $\text{-NR}''\text{-(C=Z')-NR}''\text{-}$; wherein Z' represents O, S or NR''' ; and R''' represents hydrogen, alkyl or cyano.

In a more preferred embodiment X' and X'' , independently of one another,
15 represent a linker selected from -O- , $\text{-O-CH}_2\text{-}$, -S- , -SO- , $\text{-SO}_2\text{-}$, $\text{-CH}_2\text{-}$, -NH-(CO)-NH- and/or -NH-(CO)-O- .

In a yet more preferred embodiment

X' and X'' are absent (i.e. represent single (covalent) bonds); or

X' and X'' represent -O- or $\text{-O-CH}_2\text{-}$; or

20 X' represents -O- or $\text{-O-CH}_2\text{-}$; and X'' represents -NH-(CO)-NH- or -NH-(CO)-O- .

In a twenty-first preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I-XI, wherein L represents a single (covalent) bond (i.e. L is absent).

25 In a twenty-second preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I-XI, wherein Y' and Y'' are absent (i.e. represent single (covalent) bonds).

In a more preferred embodiment L represents a single (covalent) bond (i.e. L is absent); or a group A''' which represents an aromatic monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with
30 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF_3 , CN, NO_2 , NH_2 , carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or
35 heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or

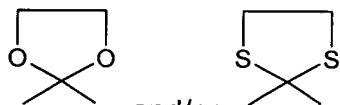
heterocyclic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

5 In an even more preferred embodiment A''' represents a phenyl, naphthyl, pyridyl, thienyl, furanyl, pyridazinyl or thiazolyl group.

In a most preferred embodiment A''' represents phenyl.

In a twenty-third preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I-XI, wherein

10 Y' and Y'', independently of one another, represent a linker selected from -O-, -O-CH₂-, -O-CH₂-CH₂-, -S-, -SO-, -SO₂-, -CH₂-, -S-CH₂-CH₂-, -CH₂-, -(C=CH₂)-, -NH-, -N(alkyl)-, -(CO)-, -(CS)-,



and/or ; and/or

15 a group of the formula -NR''-(CO)-, -NR''-(CO)-O-, -NR''-(SO₂)- and -NR''-(C=Z')-NR''-; wherein Z' represents O, S or NR'''; and R''' represents hydrogen, alkyl or cyano.

In a more preferred embodiment L represents a group A''' which represents a monocyclic or polycyclic, carbocyclic or heterocyclic group, optionally substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, 20 cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl, or with another monocyclic or polycyclic, carbocyclic or heterocyclic group, which additional monocyclic or polycyclic, carbocyclic or heterocyclic group may optionally be substituted one or more times with 25 substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, alkoxy, hydroxyalkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halo, CF₃, CN, NO₂, NH₂, carboxy, carbamoyl, amido, sulfamoyl and phenyl.

30 In an even more preferred embodiment A''' represents a phenyl, naphthyl, pyridyl, thienyl, furanyl, pyridazinyl or thiazolyl group.

In a most preferred embodiment A''' represents phenyl.

In a twenty-fourth preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I or II, wherein

----- represents a single (covalent) bond;

35 n is 2;

X' and X'' are absent (i.e. represent single (covalent) bonds); or X' and X'', independently of one another, represent -O-, -S-, -SO- or -NH-;

A' and A'' represent phenyl, pyridyl, thienyl, furanyl, pyridazinyl and/or thiazolyl; and

Y', Y'' and L represent single (covalent) bonds.

In a most preferred embodiment the azabicyclic derivative of the invention is
 5 2,2'-Bis-((±)-1-aza-bicyclo[2.2.2]oct-3-yloxy)-[5,5']-bithiazolyl;
 2,2'-Bis-((±)-1-aza-bicyclo[2.2.2]oct-3-yloxy)-[5,5']-bifuranyl;
 6,6'-Bis-((±)-1-aza-bicyclo[2.2.2]oct-3-yloxy)-[3,3']-bipyridinyl;
 6,6'-Bis-((±)-1-aza-bicyclo[2.2.2]oct-3-yloxy)-[3,3']-bipyridazinyl; or
 6-[4-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-phenyl]-pyridazin-3-ol-(1-aza-
 10 bicyclo[2.2.2]oct-3-yl);

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

In a twenty-fifth preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I-XI, wherein

15 X' and X'' are absent (i.e. represent single (covalent) bonds); or X' and X'' represent -O-, -S-, -SO-, -NH-, or -(CO)-;

A' and A'' represent phenyl, pyridyl, thienyl, furanyl, pyridazinyl and/or thiazolyl; and

20 Y', Y'' and L represent single (covalent) bonds; or Y' and Y'' represent -O-, -S-, -SO- or -NH-; and

L represents a phenyl group.

In a twenty-sixth preferred embodiment the azabicyclic derivative of the invention is a compound of Formula I or V, wherein

25 X' and X'' are absent (i.e. represent single (covalent) bonds); or X' and X'' represent -O-, -S-, -SO-, -NH-, or -(CO)-;

A' and A'' represent phenyl, pyridyl, thienyl, furanyl, pyridazinyl and/or thiazolyl; and

30 Y', Y'' and L represent single (covalent) bonds; or Y' and Y'' represent -O-, -S-, -SO- or -NH-; and

L represents a phenyl group.

In a most preferred embodiment the azabicyclic derivative of the invention is
 6,6'-Bis-[1,4]-diazabicyclo[3.2.2]nonan-1-yl-[3,3']-bipyridazinyl;

1,2-Di-[6-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-pyridazin-3-yl-thio]-benzene;

or

35 1,3-Di-[6-(1,4-diazabicyclo[3.2.2]nonan-4-yl)-pyridazin-3-yl-thio]-benzene;

or an enantiomer thereof, or a pharmaceutically-acceptable addition salt thereof, or an onium salt thereof.

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo. Thus a trihalomethyl group represents e.g. a trifluoromethyl group, a trichloromethyl group, and similar trihalo-substituted methyl groups.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C_{1-18} -alkyl), more preferred of from one to six carbon atoms (C_{1-6} -alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4} -alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a C_{1-3} -alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7} -cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy groups of the invention include methoxy and ethoxy.

In the context of this invention a hydroxy-alkoxy group designates an alkoxy group as defined above, which alkoxy group is substituted with one or more hydroxy groups. Preferred hydroxy-alkoxy groups of the invention include 2-hydroxy-ethoxy, 3-hydroxy-propoxy, 4-hydroxy-butoxy, 5-hydroxy-pentoxo and 6-hydroxy-hexoxy.

In the context of this invention a cycloalkoxy group designates a "cycloalkyl-O-" group, wherein cycloalkyl is as defined above.

In the context of this invention an alkoxy-alkyl group designates an "alkyl-O-alkyl-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkyl groups of the invention include methoxy-methyl, methoxy-ethyl, ethoxy-methyl, and ethoxy-ethyl.

In the context of this invention an alkoxy-alkoxy group designates an "alkyl-O-alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkoxy groups of the invention include methoxy-methoxy, methoxy-ethoxy, ethoxy-methoxy, and ethoxy-ethoxy.

In the context of this invention a cycloalkoxy-alkyl group designates a "cycloalkyl-O-alkyl" group, wherein cycloalkyl and alkyl are as defined above.

In the context of this invention a cycloalkoxy-alkoxy group designates a "cycloalkyl-O-alkyl-O-" group, wherein cycloalkyl and alkyl are as defined above.

In the context of this invention a mono- or polycyclic carbocyclic group is a mono- or polycyclic carbocyclic group holding carbon only as ring atom. The ring structure may in particular be aromatic (i.e. an aryl group), or saturated or partially saturated.

Preferred mono- or polycyclic carbocyclic groups of the invention include phenyl; indanyl, in particular 4-indanyl and 5-indanyl; indenyl, in particular 1-indenyl, 2-indenyl and 3-indenyl; naphthyl, in particular 1-naphthyl and 2-naphthyl; 5,6,7,8-tetrahydro-naphthyl, in particular 5,6,7,8-tetrahydro-1-naphthyl and 5,6,7,8-tetrahydro-2-naphthyl; azulenyl, in particular 1-azulenyl, 2-azulenyl and 3-azulenyl; fluorenyl, in particular 1-fluorenyl, 2-fluorenyl, 3-fluorenyl and 4-fluorenyl; and anthracenyl, in particular 1-anthracenyl and 2-anthracenyl.

The mono- or polycyclic carbocyclic group may in particular be an aromatic group (aryl). Preferred aryl groups of the invention include phenyl; indenyl, in particular 1-indenyl, 2-indenyl and 3-indenyl; naphthyl, in particular 1-naphthyl and 2-naphthyl; azulenyl, in particular 1-azulenyl, 2-azulenyl and 3-azulenyl; and anthracenyl, in particular 1-anthracenyl and 2-anthracenyl.

In the context of this invention a mono- or polycyclic heterocyclic group is a mono- or polycyclic compound, which holds one or more heteroatoms in its ring structure. The term poly-heterocyclic groups includes benzo-fused five- and six-membered heterocyclic rings containing one or more heteroatoms. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S). One or more of the ring structures may in particular be aromatic (i.e. a heteroaryl).

Preferred monocyclic heterocyclic groups of the invention include pyridyl, in particular pyrid-2-yl, pyrid-3-yl and pyrid-4-yl; thienyl, in particular thien-2-yl and thien-3-yl; furanyl, in particular furan-2-yl and furan-3-yl; pyridazinyl, in particular pyridazin-3-yl and pyridazin-4-yl; thiazolyl, in particular thiazol-2-yl, thiazol-4-yl and thiazol-5-yl; and thiadiazolyl, in particular 1,3,4-thiadiazol-2-yl, 1,3,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl and 1,2,4-thiadiazol-5-yl.

Preferred polycyclic heterocyclic of the invention include indolyl, in particular indol-2-yl and indol-3-yl; isoindolyl, in particular isoindol-2-yl; quinolinyl, in particular quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl and quinolin-6-yl; quinoxalinyl, in particular quinoxalin-2-yl and quinoxalin-3-yl; benzimidazolyl, in particular benzimidazol-2-yl; benzoxazolyl, in particular benzoxazol-2-yl; benzthiazolyl, in particular benzthiazol-2-yl; benzisothiazolyl, in particular benzisothiazol-3-yl; benztriazolyl, in particular 1,2,3-benztriazol-1-yl; imidazo[1,2-b]pyridazinyl, in particular imidazo[1,2-b]pyridazin-6-yl; and dibenzofuranyl, in particular dibenzofuran-2-yl.

Pharmaceutically Acceptable Salts

The azacyclic derivative of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the azacyclic derivative
5 of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from
10 perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzenesulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric
15 acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane
20 sulphonic acid, the naphthalene-2-sulphonate derived from naphthalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts
25 may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

30 Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysine, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well
35 known and described in the art.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts (aza-onium salts). Preferred aza-onium salts include the alkyl-onium salts, in particular the methyl- and the ethyl-onium salts; the cycloalkyl-onium salts, in particular the cyclopropyl-onium

salts; and the cycloalkylalkyl-onium salts, in particular the cyclopropyl-methyl-onium salts.

Steric Isomers

5 The azacyclic derivatives of the present invention may exist in (+) and (-) forms as well as in racemic forms (\pm). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of
10 an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or
15 camphorsulphonate) salts for example.

The azacyclic derivatives of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by
20 the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Willen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

25 Optical active compounds can also be prepared from optical active starting materials.

Methods of Preparation

The azacyclic derivatives of the invention may be prepared by conventional
30 methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound
35 of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

The present invention relates to novel azacyclic derivatives, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors (nAChR), and modulators of the monoamine receptors, in particular the biogenic amine transporters
5 such as the serotonin receptor (5-HT₁), the dopamine receptor (DAR) and the norepinephrine receptor (NER), and of the biogenic amine transporters for serotonin (5-HT), dopamine (DA) and norepinephrine (NE). Also preferred azacyclic derivatives of the invention show selective $\alpha 7$ activity, as shown in the working examples. The compounds of the present invention may in particular be agonists, partial agonists,
10 antagonists and allosteric modulators of the receptor.

Due to their pharmacological profile the azacyclic derivatives of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases, PNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neuro-degeneration, diseases
15 related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

In a preferred embodiment the azacyclic derivatives of the invention are used for the treatment of diseases, disorders, or conditions relating to the central nervous system. Such diseases or disorders includes anxiety, cognitive disorders,
20 learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, psychosis, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and
25 obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

30 In a preferred embodiment diseases, disorders, or conditions relating to the central nervous system for which the azacyclic derivatives of the invention are used are cognitive disorders, psychosis, schizophrenia and/or depression.

In another preferred embodiment the azacyclic derivatives of the invention may be useful for the treatment of diseases, disorders, or conditions associated with
35 smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

In yet another preferred embodiment the azacyclic derivatives of the invention may be useful for the treatment of endocrine disorders, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

5 In still another preferred embodiment the azacyclic derivatives of the invention may be useful for the treatment of neurodegenerative disorders, including transient anoxia and induced neurodegeneration.

10 In even another preferred embodiment the azacyclic derivatives of the invention may be useful for the treatment of inflammatory diseases, disorders, or conditions, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

15 In still another preferred embodiment the azacyclic derivatives of the invention may be useful for the treatment of mild, moderate or even severe pain of acute, chronic or recurrent character, as well as pain caused by migraine, postoperative pain, and phantom limb pain. The pain may in particular be neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.

20 Finally the azacyclic derivatives of the invention may be useful for the treatment of withdrawal symptoms caused by termination of use of addictive substances. Such addictive substances include nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol. Withdrawal from addictive substances is in general a traumatic experience characterised by anxiety and frustration, anger, anxiety, difficulties in concentrating, restlessness, decreased heart rate and increased appetite and weight gain.

25 In this context "treatment" covers treatment, prevention, prophylactics and alleviation of withdrawal symptoms and abstinence as well as treatment resulting in a voluntary diminished intake of the addictive substance.

30 In another aspect, the azacyclic derivatives of the invention are used as diagnostic agents, e.g. for the identification and localisation of nicotinic receptors in various tissues.

Pharmaceutical Compositions

35 In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the azacyclic derivatives of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a

pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the azacyclic derivative together with one or more
5 pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by
10 any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by a person skilled in the art by use
15 of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing
20 Co., Easton, PA).

The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical
25 compositions containing from about 0.1 to about 500 mg of active ingredient per individual dose, preferably from about 1 to about 100 mg, most preferred from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1
30 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about 100 mg/kg/day p.o.

Methods of Therapy

35 Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases, PNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neuro-degeneration, diseases related to inflammation,

pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

In another aspect the invention provides methods of the treatment, prevention or alleviation of diseases or disorders or conditions of a living animal body, including a human, which disease or disorder is responsive to the action of a monoamine receptor modulator, and which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of the azacyclic derivative of the invention.

In the context of this invention the term "treating" covers treatment, prevention, prophylaxis or alleviation, and the term "disease" covers illnesses, diseases, disorders and conditions related to the disease in question.

It is at present contemplated that a suitable dosage lies within the range of from about 0.1 to about 500 milligram of active substance daily, more preferred of from about 10 to about 70 milligram of active substance daily, administered once or twice a day, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

20

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

25 Example 1

Preparatory Example

General remarks: All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

Method A

(±)-3-(5-Bromo-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane fumaric acid salt
(Intermediate compound)

35 To a mixture of (±)-3-quinuclidinol (10.32 g; 81.1 mmol), 2,5-dibromothiazole (19.7 g; 81.1 mmol) and DMF (150 ml), was added: sodium hydride, 60% with oil (6.49 g; 162 mmol), at 0°C for 1.5 hours. Aqueous sodium hydroxide (100 ml; 1M) was added. The mixture was extracted with ethyl acetate (3 x 100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia

(89:10:1) gave the title compound. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 6.7 g (28%). Mp. 157.8-162.1°C.

5 2,2'-Bis-((±)-1-aza-bicyclo[2.2.2]oct-3-yloxy)-[5,5']-bithiazolyl fumaric acid salt (Compound A1)

A mixture of (±)-3-(5-bromo-thiazol-2-yloxy)-1-aza-bicyclo[2.2.2]octane (1.00 g; 3.46 mmol), Pd(PPh₃)₄ (0.20 g; 0.17 mmol), hexamethylditin (0.58 g; 1.77 mmol) and dioxane (30 ml) was stirred for 40 hours. Aqueous sodium hydroxide (100 ml; 1M) was added. The mixture was extracted with ethyl acetate (3 x 100 ml). Chromatography on silica gel with dichloromethane, methanol and conc. ammonia (89:10:1) gave the title compound. Yield 0.22 g (15%). The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp. 189.7°C.

15

Method B

1,2-Di-[6-(1,4-diaza-bicyclo[3.2.2]nonan-4-yl)-pyridazin-3-yl-thio]-benzene fumaric acid salt (Compound B1)

A mixture of 4-(6-chloro-pyridazin-3-yl)-1,4-diazabicyclo[3.2.2]nonane (0.63 g; 2.6 mmol), 1,2-benzenedithiol (0.15 g; 1.1 mmol) and dioxane was stirred at reflux for 8 hours. Aqueous sodium hydroxide (5 ml; 4M) was added. The mixture was extracted with dichloromethane (3 x 5 ml). Chromatography on silica gel with dichloromethane, 10% methanol and 1% aqueous ammonia as solvent gave the title compound as an oil. Yield 0.20 g; 33%. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp. 134-138°C.

1,3-Di-[6-(1,4-diaza-bicyclo[3.2.2]nonan-4-yl)-pyridazin-3-yl-thio]benzene fumaric acid salt (Compound B2)

30 The title compound was prepared according to Method D from 1,3-benzenedithiol. Mp. 62°C.

6,6'-Bis-[1,4]-diaza-bicyclo[3.2.2]nonan-1-yl-[3,3']-bipyridazinyl fumaric acid salt (Compound B3)

35 A mixture of 4-(6-bromo-pyridazin-3-yl)-1,4-diazabicyclo[3.2.2]nonane (0.49 g; 1.7 mmol), diethyl-3-pyridylborane (0.38 g; 2.6 mmol), aqueous potassium carbonate (2.6 ml; 5.1 mmol), Pd(PPh₃)₄ (59 mg; 0.051 mmol), 1,3-propandiol (0.37 ml; 5.1 mmol) and dioxane (5 ml) was stirred at reflux for 15 hours. Aqueous sodium hydroxide (10 ml; 4M) was added. The mixture was extracted with dichloromethane (3

x 5 ml). Chromatography on silica gel with dichloromethane, 10% methanol and 1% aqueous ammonia as solvent gave the title compound as an oil. Yield 93 mg; 27%. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Mp. > 300°C.

5

Example 2

Biological Activity

In vitro Inhibition of ^3H - α -Bungarotoxine Binding in Rat Brain

In this example the affinity of the compounds of the invention for binding to
10 α_7 -subtype of nicotinic receptors is determined.

α -Bungarotoxine is a peptide isolated from the venom of the Elapidae snake *Bungarus multicinctus*. It has high affinity for neuronal and neuromuscular nicotinic receptors, where it acts as a potent antagonist. ^3H - α -Bungarotoxine labels nicotinic acetylcholine receptors formed by the α_7 subunit isoform found in brain and
15 the α_1 isoform in the neuromuscular junction.

Tissue preparation

Preparations are performed at 0-4°C. Cerebral cortices from male Wistar rats (150-250 g) are homogenised for 10 seconds in 15 ml of 20 mM Hepes buffer
20 containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM MgSO_4 and 2.5 mM CaCl_2 (pH 7.5) using an Ultra-Turrax homogeniser. The tissue suspension is subjected to centrifugation at 27,000 x g for 10 minutes. The supernatant is discarded and the pellet is washed twice by centrifugation at 27,000 x g for 10 minutes in 20 ml of fresh buffer, and the final pellet is then re-suspended in fresh buffer containing 0.01% BSA
25 (35 ml per g of original tissue) and used for binding assays.

Assay

Aliquots of 500 μl of homogenate are added to 25 μl of test solution and 25 μl of ^3H - α -bungarotoxine (2 nM, final concentration) and mixed and incubated for 2
30 hours at 37°C. Non-specific binding is determined using (-)-nicotine (1 mM, final concentration). After incubation, the samples are added 5 ml of ice-cold Hepes buffer containing 0.05% PEI and poured directly onto Whatman GF/C glass fibre filters (pre-soaked in 0.1% PEI for at least 6 hours) under suction, and immediately washed with 2 x 5 ml ice-cold buffer.

35 The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

The test value is given as an IC_{50} (the concentration of the test substance which inhibits the specific binding of ^3H - α -bungarotoxin by 50%).

The results of these experiments are presented in Table 1 below.

Table 1**Inhibition of ^3H - α -Bungarotoxine Binding**

Compound No.	IC ₅₀ (μM)
A1	0.20